Kineretä

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DESCRIPTION

Kineret™ (anakinra) is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). Kineret™ differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. Kineret™ consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an *E. coli* bacterial expression system.

Kineret™ is supplied in single use 1 mL prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative-free solution for daily subcutaneous (SC) administration. Each 1 mL prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP.

CLINICAL PHARMACOLOGY

Kineret™ blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs.[1]

IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses. IL-1 has a broad range of activities including cartilage degradation by its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption.[2] The levels of the naturally occurring IL-1Ra in synovium and synovial fluid from rheumatoid arthritis (RA) patients are not sufficient to compete with the elevated amount of locally produced IL-1.[3,4,5]

Pharmacokinetics

The absolute bioavailability of Kineret™ after a 70 mg SC bolus injection in healthy subjects (n=11) is 95%. In subjects with RA, maximum plasma concentrations of Kineret™ occurred 3 to 7 hours after SC administration of anakinra at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of Kineret™ was observed after daily SC doses for up to 24 weeks.

The influence of demographic covariates on the pharmacokinetics of Kineret™ was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily SC injection of Kineret™ at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated Kineret™ clearance increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance

and body weight, gender and age were not significant factors for mean plasma clearance.

Patients with Renal Impairment: The mean plasma clearance of Kineret™ decreased 70-75% in normal subjects with severe or end stage renal disease (defined as creatinine clearance less than 30 mL/minute, as estimated from serum creatinine levels[6]). No formal studies have been conducted examining the pharmacokinetics of Kineret™ administered subcutaneously in rheumatoid arthritis patients with renal impairment.

Patients with Hepatic Dysfunction: No formal studies have been conducted examining the pharmacokinetics of Kineret™ administered subcutaneously in rheumatoid arthritis patients with hepatic impairment.

CLINICAL STUDIES

The safety and efficacy of Kineret™ have been evaluated in three randomized, double-blind, placebo-controlled trials of 1392 patients ≥ 18 years of age with active rheumatoid arthritis (RA). An additional fourth study was conducted to assess safety. In the efficacy trials, Kineret™ was studied in combination with other disease-modifying antirheumatic drugs (DMARDs) (studies 1 and 2) or as a monotherapy (study 3).

Study 1 evaluated 501 patients with active RA who had been on a stable dose of methotrexate (MTX) (10 to 25 mg/week) for at least 8 weeks. In addition, they had at least 6 swollen/painful and 9 tender joints and either a C-reactive protein (CRP) of ≥1.5 mg/dL or an erythrocyte sedimentation rate (ESR) of ≥ 28 mm/hr. Patients were randomized to Kineret or placebo in addition to their stable doses of MTX.

Study 2 evaluated 419 patients with active RA who had received MTX for at least 6 months including a stable dose (15 to 25 mg/week) for at least 3 consecutive months prior to enrollment. Patients were randomized to receive placebo or one of five doses of Kineret ™ SC daily for 12 to 24 weeks in addition to their stable doses of MTX.

Study 3 evaluated 472 patients with active RA and had similar inclusion criteria to Study 1 except that these patients had received no DMARD for the previous 6 weeks or during the study.[7] Patients were randomized to receive either Kineret™ or placebo. Patients were DMARD-naïve or had failed no more than 3 DMARDs.

Study 4 was a placebo-controlled, randomized trial designed to assess the safety of Kineret™ in 1414 patients receiving a variety of concurrent medications for their RA including some DMARD therapies, as well as patients who were DMARD-free. The TNF blocking agents etanercept and infliximab were specifically excluded. Concurrent DMARDS included MTX, sulfasalazine, hydrochloroquine, gold, penicillamine, leflunomide, and azathioprine. Unlike studies 1, 2 and 3, patients predisposed to infection due to a history of underlying disease such as pneumonia, asthma, controlled diabetes, and chronic

obstructive pulmonary disease (COPD) were also enrolled. (See **ADVERSE REACTIONS**-Infections).

In Studies 1, 2, and 3, the improvement in signs and symptoms of RA was assessed using the American College of Rheumatology (ACR) response criteria (ACR_{20}, ACR_{50}, ACR_{70}). In all three studies, patients treated with Kineret™ were more likely to achieve an ACR_{20} or higher magnitude of response (ACR_{50} and ACR_{70}) than patients treated with placebo (Table 1). The treatment response rates did not differ based on gender or ethnic group. The results of the ACR component scores in Study 1 are shown in Table 2.

Most clinical responses, both in patients receiving placebo and patients receiving Kineret™, occurred within 12 weeks of enrollment.

Table 1. Percent of Patients with ACR Responses in Studies 1 and 3

	Study 1 (Patients on MTX)		Study 3 (No DMARDs)		
Response	Placebo (n=251)	Kineret™ 100 mg/day (n=250)	Placebo (n=119)	Kineret™ 75 mg/day (n=115)	Kineret™ 150mg/day (n=115)
ACR 20					
Month 3	24%	34% [a]	23%	33%	33%
Month 6	22%	38% [c]	27%	34%	43% [a]
ACR 50					
Month 3	6%	13% [b]	5%	10%	8%
Month 6	8%	17% [b]	8%	11%	19% [a]
ACR 70					
Month 3	0%	3% [a]	0%	0%	0%
Month 6	2%	6% [a]	1%	1%	1%

[a] $p<0.05$, Kineret™ versus placebo
[b] $p<0.01$, Kineret™ versus placebo
[c] $p<0.001$, Kineret™ versus placebo

Table 2. Effect of Kineret on Median ACR Component Scores in Study 1

	Placebo/MTX (N = 251)		Kineret™/MTX 100 mg/day (N = 250)	
Parameter (median)	Baseline	Month 6	Baseline	Month 6
Patient Reported Outcomes				
Disability index[a]	1.38	1.13	1.38	1.00
Patient global assessment[b]	51.0	41.0	51.0	29.0
Pain[b]	56.0	44.0	63.0	34.0
Objective Measures				
ESR (mm/hr)	35.0	32.0	36.0	19.0
CRP (mg/dL)	2.2	1.6	2.2	0.5
Physician's Assessments				
Tender/painful joints[c]	20.0	11.0	23.0	9.0
Physician global assessment[b]	59.0	31.0	59.0	26.0
Swollen joints[d]	18.0	10.5	17.0	9.0

[a] Health assessment questionnaire; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[b] Visual analog scale; 0 = best, 100 = worst

[c] Scale 0 to 68

[d] Scale 0 to 66

INDICATIONS AND USAGE

Kineret™ is indicated for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs). Kineret™ can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents (See **WARNINGS**).

CONTRAINDICATIONS

Kineret™ is contraindicated in patients with known hypersensitivity to *E.coli*-derived proteins, Kineret™, or any components of the product.

WARNINGS

KINERETÔ HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF SERIOUS INFECTIONS (2%) vs. PLACEBO (< 1%). ADMINISTRATION OF KINERETÔ SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. TREATMENT WITH KINERETÔ SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS. THE SAFETY AND EFFICACY OF KINERETä IN IMMUNOSUPPRESSED PATIENTS OR IN PATIENTS WITH CHRONIC INFECTIONS HAVE NOT BEEN EVALUATED. THE SAFETY OF KINERETÔ USED IN COMBINATION WITH TNF BLOCKING AGENTS HAS NOT BEEN ESTABLISHED. PRELIMINARY DATA SUGGEST A HIGHER RATE OF SERIOUS INFECTIONS (7%, 4/58) WHEN KINERETÔ AND ETANERCEPT ARE USED IN COMBINATION COMPARED WITH WHEN KINERETÔ IS USED ALONE. IN THIS COMBINATION STUDY NEUTROPENIA (NEUTROPHIL COUNT £ 1000/mm^3) WAS OBSERVED IN 3% OF PATIENTS (2/58). USE OF KINERETÔ WITH TNF BLOCKING AGENTS SHOULD ONLY BE DONE WITH EXTREME CAUTION AND WHEN NO SATISFACTORY ALTERNATIVES EXIST.

PRECAUTIONS

General

Hypersensitivity reactions associated with Kineret™ administration are rare. If a severe hypersensitivity reaction occurs, administration of Kineret™ should be discontinued and appropriate therapy initiated.

Immunosuppression

The impact of treatment with Kineret™ on active and/or chronic infections and the development of malignancies is not known. (See **WARNINGS, ADVERSE REACTIONS, Infections and Malignancies**).

Immunizations

No data are available on the effects of vaccination in patients receiving Kineret™. Live vaccines should not be given concurrently with Kineret™. No data are available on the secondary transmission of infection by live vaccines in patients receiving Kineret™ **(**See **Precautions, Immunosuppression).** Since Kineret™ interferes with normal immune response mechanisms to new antigens such as vaccines, vaccination may not be effective in patients receiving Kineret™.

Information for Patients

If a physician has determined that a patient can safely and effectively receive Kineret™ at home, patients and their caregivers should be instructed on the proper dosage and administration of Kineret™. All patients should be provided with the “Information for Patients and Caregivers” insert. While this “Information for Patients and Caregivers” insert provides information about the product and its

use, it is not intended to take the place of regular discussions between the patient and healthcare provider.

Patients should be informed of the signs and symptoms of allergic and other adverse drug reactions and advised of appropriate actions. Patients and their caregivers should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, and drug product. A puncture-resistant container for the disposal of used syringes should be available to the patient. The full container should be disposed of according to the directions provided by the healthcare professional.

Laboratory Tests

Patients receiving Kineret™ may experience a decrease in neutrophil counts. In the placebo-controlled studies, 8% of patients receiving Kineret™ had decreases in neutrophil counts of at least 1 World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Six Kineret™-treated patients (0.3%) experienced neutropenia (ANC $\leq 1 \times 10^9$/L). This is discussed in more detail in the Adverse Events-Hematologic Events section. Neutrophil counts should be assessed prior to initiating Kineret™ treatment, and while receiving Kineret™, monthly for 3 months, and thereafter quarterly for a period up to 1 year.

Drug Interactions

No drug-drug interaction studies in human subjects have been conducted. Toxicologic and toxicokinetic studies in rats did not demonstrate any alterations in the clearance or toxicologic profile of either methotrexate or Kineret™ when the two agents were administered together.

Carcinogenesis, Mutagenesis, And Impairment Of Fertility

Kineret™ has not been evaluated for its carcinogenic potential in animals. Using a standard *in vivo* and *in vitro* battery of mutagenesis assays, Kineret™ did not induce gene mutations in either bacteria or mammalian cells. In rats and rabbits, Kineret™ at doses of up to 100-fold greater than the human dose had no adverse effects on male or female fertility.

Pregnancy Category B

Reproductive studies have been conducted with Kineret™ on rats and rabbits at doses up to 100 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Kineret™ should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether Kineret™ is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if Kineret™ is administered to nursing women.

Pediatric Use

The safety and efficacy of Kineret™ in patients with juvenile rheumatoid arthritis (JRA) have not been established.

Geriatric Use

A total of 653 patients ≥ 65 years of age, including 135 patients ≥ 75 years of age, were studied in clinical trials. No differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

ADVERSE REACTIONS

The most serious adverse reactions were:

- Serious Infections - see **WARNINGS**
- Neutropenia, particularly when used in combination with TNF blocking agents – see **WARNINGS**

The most common adverse reaction with Kineret™ is injection site reactions. These reactions were the most common reason for withdrawing from studies.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to Kineret™ in 2606 patients, including 1812 exposed for at least 6 months and 570 exposed for at least one year. Studies 1 and 4 used the recommended dose of 100 mg per day. The patients studied were representative of the general population of patients with rheumatoid arthritis.

Injection-Site Reactions

The most common and consistently reported treatment-related adverse event associated with Kineret™ is injection-site reaction (ISR). The majority of ISRs were reported as mild. These typically lasted for 14 to 28 days and were characterized by 1 or more of the following: erythema, ecchymosis, inflammation, and pain. In Studies 1 and 4, 71% of patients developed an ISR, which was typically reported within the first 4 weeks of therapy. The development of ISRs in patients who had not previously experienced ISRs was uncommon after the first month of therapy.

Infections

In Studies 1 and 4 combined, the incidence of infection was 40% in the Kineret™ -treated patients and 35% in placebo-treated patients. The incidence of serious infections in studies 1 and 4 was 1.8% in Kineret™-treated patients and 0.6% in placebo-treated patients over 6 months. These infections consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections, rather than unusual, opportunistic, fungal, or viral infections. Patients with asthma appeared to be at higher risk of developing serious infections; Kineret™ 5% versus placebo <1%. Most patients continued on study drug after the infection resolved. There were no on-study deaths due to serious infectious episodes in either study.

In a study in which patients were receiving both etanercept and Kineret™ for up to 24 weeks, the incidence of serious infections was 7%. These infections consisted of bacterial pneumonia (2 cases) and cellulitis (2 cases), which recovered with antibiotic treatment.

Malignancies

Twenty-one malignancies of various types were observed in 2531 RA patients treated in clinical trials with Kineret™ for up to 50 months. The observed rates and incidences were similar to those expected for the population studied.

Hematologic Events

In placebo-controlled studies with Kineret™, treatment was associated with small reductions in the mean values for total white blood count, platelets, and absolute neutrophil blood count (ANC), and a small increase in the mean eosinophil differential percentage.

In all placebo-controlled studies, 8% of patients receiving Kineret™ had decreases in ANC of at least 1 WHO toxicity grade, compared with 2% of placebo patients. Six Kineret™-treated patients (0.3%) developed neutropenia (ANC $\leq 1 \times 10^9$/L). Additional patients treated with Kineret™ plus etanercept (2/58, 3%) developed ANC $\leq 1 \times 10^9$/L. While neutropenic, one patient developed cellulitis and the other patient developed pneumonia. Both patients recovered with antibiotic therapy.

Immunogenicity

In Study 4, 28% of patients tested positively for anti-Kineret™ antibodies at month 6 in a highly sensitive, Kineret™-binding biosensor assay. Of the 1274 subjects with available data, <1% (n = 9) were seropositive in a cell-based bioassay for antibodies capable of neutralizing the biologic effects of Kineret™. None of these 9 subjects were positive for neutralizing antibodies at more than 1 time point, and all of these subjects were negative for neutralizing antibodies by 9 months. No correlation between antibody development and clinical response or adverse events was observed. The long-term immunogenicity of Kineret™ is unknown.

Antibody assay results are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Kineret™ with the incidence of antibodies to other products may be misleading.

Other Adverse Events

Table 3 reflects adverse events in Studies 1 and 4, that occurred with a frequency of ≥ 5% and a higher frequency in Kineret™-treated patients.

Table 3. Percent of RA Patients Reporting Adverse Events (Studies 1 and 4)

Preferred Term	Placebo (N = 534)	Kineret™ 100 mg/day (N = 1366)
Injection Site Reaction	28 %	71 %
Infection	35 %	40 %
URI	13 %	13 %
Sinusitis	4 %	6 %
Influenza-Like Symptoms	4 %	5 %
Other	23 %	26 %
Headache	9 %	12 %
Nausea	6 %	8 %
Diarrhea	5 %	7 %
Sinusitis	6 %	7 %
Influenza-Like Symptoms	5 %	6 %
Pain Abdominal	4 %	5 %

OVERDOSAGE

There have been no cases of overdose reported with Kineret™ in clinical trials of RA. In sepsis trials no serious toxicities attributed to Kineret™ were seen when administered at mean calculated doses of up to 35 times those given patients with RA over a 72-hour treatment period.

DOSAGE AND ADMINISTRATION

The recommended dose of Kineret™ for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. Higher doses did not result in a higher response. The dose should be administered at approximately the same time every day. Kineret™ is provided in single-use 1 mL prefilled glass syringes. Instructions on appropriate use should be given by the health care professional to the patient or care provider. Patients or care providers should not be allowed to administer Kineret™ until he/she has demonstrated a thorough understanding of procedures and an ability to inject the product. After administration of Kineret™, it is essential to follow the proper procedure for disposal of syringes and needles. See the "Information for Patients and Caregivers" leaflet for detailed instructions on the handling and injection of Kineret™.

Visually inspect the solution for particulate matter and discoloration before administration. If particulates or discoloration are observed, the prefilled syringe should not be used.

Administer only 1 dose (the entire contents of 1 prefilled glass syringe) per day. Discard any unused portions; Kineret™ contains no preservative. Do not save unused drug for later administration.

HOW SUPPLIED

Kineret™ is supplied in single-use preservative free, 1 mL prefilled glass syringes with 27 gauge needles. Each prefilled glass syringe contains 0.67 mL (100 mg) of anakinra. Kineret™ is dispensed in packs containing 7 syringes. It is also available in a 4x7 syringe dispensing pack (28 syringes). The NDC number for Kineret™ is 55513-177-07.

Storage

Do not use Kineret™ beyond the expiration date shown on the carton. Kineret™ should be stored in the refrigerator at 2° to 8°C (36° to 46°F). **DO NOT FREEZE OR SHAKE.** Protect from light.

References

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